REMARKS

Claims 18 and 25-35 are pending and stand rejected under 35 U.S.C. § 103 as being unpatentable over Wedeking et al. (U.S. Patent No. 6,093,382; "Wedeking") in view of Sinkule et al. (European Patent Application No. 0 282 057; "Sinkule"). Applicants address each basis for the rejection below.

Rejection under 35 U.S.C. § 103

Claims 18 and 25-35 stand rejected under 35 U.S.C. § 103 as being obvious over Wedeking in view of Sinkule. In particular, the Office states (pages 3 and 4):

> [A]t the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the IgG antibody of Sinkule et al. for the small molecule of Wedeking et al. with the expectation of success for targeting the conjugate to a desired tumor cell for uptake with a high degree of specificity as Sinkule et al. teaches that IgG can be successfully used to target desired tumor cells upon conjugation to a radionuclide-folate analogue species without interfering with folate targeting. Therefore, the conjugates of the combined disclosures encompass the conjugates of the instant claims and are capable of the same functions and have the same properties, such as dual binding.

Applicants respectfully traverse this basis for rejection.

Two independent claims, claims 18 and 31, are pending, and these claims are directed to Applicants' discovery that both an antibody component and a non-cytotoxic folate component of a complex can be used to target a radionuclide to a malignant cell. In particular, claim 18 is directed to a method of targeting a radionuclide to a malignant cell within a subject, where the malignant cell expresses a tumor associated antigen and expresses folate binding protein. This method involves (i) coupling an antibody, antibody fragment, or antibody construct having affinity for the tumor associated antigen to at least one non-cytotoxic folate to form a dual binding conjugate, (ii) coupling the radionuclide to the dual binding conjugate, and (iii) administering the radionuclide coupled to the dual binding conjugate to the subject. Claim 31 is directed to a conjugate consisting of (i) a

radionuclide, (ii) an antibody, antibody fragment, or antibody construct, with affinity for a tumor associated antigen, and (iii) at least one non-cytotoxic folate.

Applicants submit that, contrary to the Office's assertion, Sinkule does not teach "that IgG can be successfully used to target desired tumor cells upon conjugation to a radionuclide-folate analogue species without interfering with folate targeting" (emphasis added) because Sinkule fails to describe targeting the conjugate to a malignant cell using the folate component of a complex. Instead, Sinkule explicitly states that the antibody component targets the complex to the tumor. For example, at column 5, lines 13-15, Sinkule states (emphasis original):

> The therapeutic activity of the conjugate in vivo is localized by the antibody, which is selected for specificity for the target cell or biomaterial.

While the conjugate of Sinkule may contain folic acid analogues, these folic acid analogues are described as chemotherapeutic agents (see column 2, lines 26-30). As such, the folic acid analogue forms part of the "therapeutic activity" of the conjugate that is localized by the antibody. As the antibody is targeting the complex, one simply cannot conclude that the presence of the antibody does not interfere with folate targeting; Sinkule does not describe folate targeting.

Moreover, as noted in the last reply, adding a large molecule, such as bovine serum albumin (BSA), to a folate-containing complex, can interfere with the targeting ability of the folate. The specification states (at page 1, lines 22-27):

> In a previous study, Shinoda et al. (1998) evaluated folate conjugated bovine serum albumin (BSA) labelled with the radionuclide indium-111, and found that there was a significant difference in pharmacokinetics and biodistribution of non-folate compared to folate labelled BSA. A high liver uptake and rapid blood clearance indicated that the folate labelled version of ^{111}In-BSA was not particularly suitable for radionuclide delivery to tumour cells expressing folate binding protein.

BSA with a mass of about 66,000 amu, like an antibody (150,000 amu for IgG), is a large protein, and Applicants submit that one skilled in the art would expect to observe similar effects if a folate were added to an antibody-radionuclide complex. Namely, Applicants submit that there was no indication in the art that a large molecule, like an antibody, could be complexed with a folate with the expectation that the folate would maintain its targeting ability.

The Office dismisses Applicants' argument based on the Shinoda BSA experiments summarized in the specification, stating (page 5; emphasis original):

> The reference of Shinoda et al. teaches that the **low vascular permeability of BSA** into solid tumor tissue and inhibition of folate-mediated ^{111}In-folate-BSA uptake by tumor cells from the blood may be the rate-limiting factor of distribution (Shinoda et al. abstract). This is opposed to the reference of Sinkule et al. which teaches that targeting antibodies are included in the conjugate to target the conjugate to a desired tumor cell for uptake with a high degree of specificity, without interfering with folate targeting, while facilitating the destruction of cancerous cells and minimizing the damage to normal cells.

As an initial matter, Applicants, for the reasons explained above, submit that Sinkule does not describe folate targeting or use of folate to target a conjugate. The antibody targets the Sinkule conjugate.

Further, Applicants submit that the passage of Shinoda cited by the Office does not negate the assertion that Shinoda indicates that the presence of a large protein (BSA) affects the ability of a folate to target a tumor. The folate in Shinoda's BSA-folate-radionuclide complex cannot be considered to maintain its ability to target the radionuclide to the tumor because, once BSA is added to the complex, presence of the folate is not sufficient for the complex to be localized to the tumor. In contrast, Applicants' claims are directed to conjugates in which a non-cytotoxic folate maintains its targeting ability when complexed with an antibody and a radionuclide.

Applicants, surprisingly, have shown that both the antibody component and the non-cytotoxic folate component of a conjugate can target the conjugate to a malignant cell. In this regard, Applicants direct the Office's attention to Examples 5 and 6 of the specification. In particular, in Example 6, at page 14, lines 18-23, the specification states:

> Folate-antibody-radionuclide conjugates show a significant binding to folate binding protein (FBP) on cells indicating that these conjugates may be used to target FBP-expressing tumour cells in vivo. Also, as demonstrated by specific binding of folate-TP-3-IgG-^{125}I to antigen positive OHS cells as well as FBP-positive HELA-S3 and OVCAR-3 cells, folate-antibody-radionuclide conjugates can possess dual binding ability.

The dual binding ability of the conjugates encompassed by the present claims is neither taught nor suggested by Sinkule.

The other cited reference, Wedeking, describes targeting of small molecules using a folate (see columns 27-32). As Applicants have previously noted, and as explained above in reference to Shinoda, success in targeting a small molecule using a folate does not render obvious a conjugate where the folate retains its targeting ability when complexed to a large protein such as an antibody.

For all the above reasons, the combination of Sinkule with Wedeking fails to render a dual binding conjugate containing a radionuclide, an antibody, and a non-cytotoxic folate obvious. The obviousness rejection of claims 18 and 25-35 should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office Action for three (3) months, to and including July 21, 2010, and an authorization to charge the required extension fee to Deposit Account No. 03-2095.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 21 July 2010

Jan N. Tittel, Ph.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045